(12) UK Patent Application (19) GB (11) 2 031 408 A

(21) Application No **7928275**
(22) Date of filing **14 Aug 1979**
(23) Claims filed **14 Aug 1979**
(30) Priority data
(31) **53/101549**
(32) **21 Aug 1978**
(33) **Japan (JP)**
(43) Application published **23 Apr 1980**
(51) **INT CL³**
C07D 233/56 A61K 31/415
(52) Domestic classification
C2C 1410 200 215 220 22Y 246 250 252 25Y 271 281 282 29X 29Y 30Y 321 322 32Y 332 342 34Y 364 365 366 367 368 36Y 373 37Y 43X 450 453 455 45Y 464 465 490 500 509 50Y 552 579 594 601 613 620 621 623 624 628 62X 658 65X 660 661 662 668 680 681 708 802 80Y AA BK KF KK LR LS MM NJ QT WK
(56) Documents cited
None
(58) Field of search
C2C
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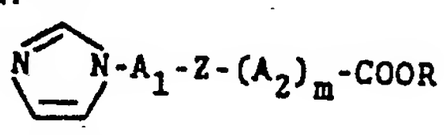
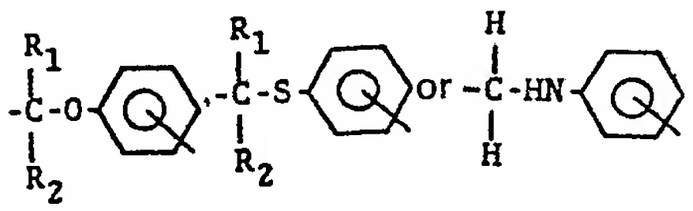
(54) Imidazole derivatives

(57) Imidazole derivatives of the formula:



wherein R is a hydrogen atom or an alkyl group, A_1 and A_2, which may be the same or different, each is an alkylene or an alkenylene group, m is 0 or 1, and Z is



wherein R_1 and R_2, which may be the same or different, each is a hydrogen atom or an alkyl group, and the terminal carbon atom bonded to the hetero atom of Z may be bonded to either A_1 or A_2 or COOR group (in the case of m being 0); and pharmaceutically acceptable salts thereof have a strong inhibitory effect on thromboxane synthetase from human or bovine platelet microsomes, and are useful as therapeutically active agents for treatment of inflammation, hypertension, thrombus, cerebral apoplexy and asthma, e.g. in the form of a pharmaceutical composition.

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SPECIFICATION

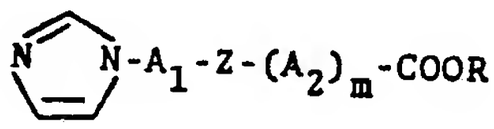
Imidazole derivatives

This invention relates to imidazole derivatives.

Up to now, of the compounds having an imidazole skeleton, it has been reported that imidazole, 1-alkyl-imidazoles, 1-benzylimidazole, 1-[2-isopropylphenyl] imidazole and their analogues possess an inhibitory action for thromboxane synthetase [*Prostaglandins,* Vol. 13, No. 4, 611—(1977), *BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,* Vol. 80, No. 1, 236—(1978)]. However, since imidazole and 1-lower alkylimidazoles show only a very weak inhibitory effect, these compounds do not provide practically effective medicines. On the other hand, 1-benzylimidazole, 1-(2-isopropylphenyl)imidazole, 1-higher alkylimidazoles such as 1-nonylimidazole and 1-decylimidazole, and their analogues show a strong inhibitory effect as compared with the imidazole and 1-lower alkylimidazoles, but the inhibitory potency of these compounds is still far from satisfactory for their use as therapeutically active agents. In addition, the action of these compounds is not a specific inhibitory action for thromboxane synthetase because they exhibit inhibitory actions for both thromboxane synthetase and cyclooxygenase. Furthermore, in the case of 1-(2-isopropylphenyl)imidazole, the preparation of this compound is difficult, so that the problem of industrial application still remains unsettled.

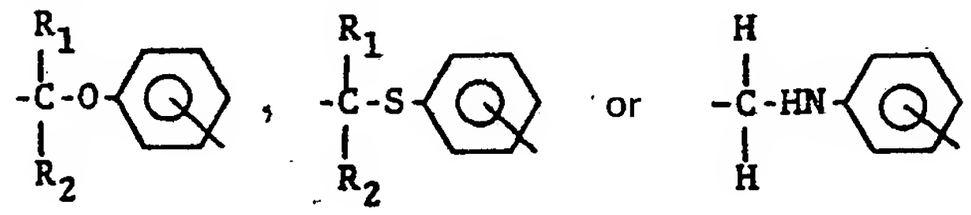
An object of this invention is to provide compounds which exhibit a strong and specific inhibitory effect on thromboxane synthetase and which are therapeutically useful.

Accordingly, the invention resides in an imidazole derivative of the formula (I).



(I)

wherein R is a hydrogen atom or an alkyl group, A_1 and A_2, which may be the same or different, each is an alkylene or an alkenylene group, m is 0 or 1, and Z is



wherein R_1 and R_2, which may be the same or different, each is a hydrogen atom or an alkyl group, and the terminal carbon atom bonded to the hetero atom of Z may be bonded to A_1 or A_2 or COOR (in the case of m being 0); or a pharmaceutically acceptable salt thereof.

The term "alkyl" as used herein means a straight or branched chain alkyl group having 1 to 6 carbon atoms.

The term "alkoxy" as used herein means a straight or branched chain alkoxyl group having 1 to 6 carbon atoms.

The term "alkylene" or "alkenylene" as used herein means straight or branched chain alkylene or alkenylene group having 1 to 8 carbon atoms unless otherwise indicated.

The term "acid residual group" as used herein means a halogen atom or an acid residual group formed from an organic or inorganic sulfonic acid.

The symbol "Y" as used herein means the carbon atom which is bonded to R_1 and R_2 of Z and which may be bonded to either A_1 or A_2.

The imidazole derivatives of the formula (I) of this invention exhibit an inhibitory action for thromboxane synthetase from human or bovine platelet microsomes. That is, the imidazole derivatives of this invention inhibit conversion of PROSTAGLANDIN H_2 into THROMBOXANE B_2 via THROMBOXANE A_2 which is an unstable intermediate and which is known to induce irreversible platelet aggregation and to contract smooth muscle and particularly blood vessel muscle. [*Nature,* Vol. 261, No. 6, 17—(1976)]. These facts demonstrate that the imidazole derivatives of this invention inhibit the biosynthesis of thromboxane A_2, and are thus useful for the treatment of diseases caused by thromboxane A_2, such as inflammation, hypertension, thrombus, cerebral apoplexy and asthma.

The inhibitory action of the imidazole derivatives of this invention can be confirmed by determination of thromboxane B_2 produced by thromboxane synthetase from prostaglandin H_2 via thromboxane A_2. Furthermore, the inhibitory action of the imidazole derivatives of this invention can be confirmed by determination of the inhibitory effect on platelet aggregation caused by arachidonic acid (arachidonic acid is converted to prostaglandin H_2 by cyclooxygenase, and prostaglandin H_2 is converted to thromboxane B_2 via thromboxane A_2 which is known to induce platelet aggregation as described above).

Further still, the inhibitory action of the imidazole derivatives of this invention can be confirmed by determination of the inhibitory effect on sudden death caused by arachidonic acid.

The imidazole derivatives of this invention are characterized by the presence of the side chain having a methyl-oxy-, -thio- or -amino-phenyl moiety, which is attached at 1-position of imidazole

skeleton, and which has a carboxy group or an alkoxycarbonyl group at ω-position of the side chain or on the phenyl ring (in the case that m is 0 when Y is bonded to A_1).

In the imidazole derivatives of the formula (I) above of this invention, the potency of the inhibitory action for thromboxane synthetase varies significantly according to whether Y is bonded to A_1 or A_2, that is, when Y is bonded to A_1, A_1 is to have an alkylene or an alkenylene group containing one or more linear carbon atoms to provide a strong inhibitory effect, and in this case, it is most desirable that m is 0 or A_2 is an alkylene or an alkenylene group having 1 to 3 carbon atoms. On the other hand, when Y is bonded to A_2 or COOR group (in the case of m being 0), the compounds wherein the phenyl group directly attached at 1-position of the imidazole are extremely weak in their inhibitory activity on thromboxane synthetase.

The position of substitution on the phenyl ring may be in any of the o-, m- or p-position, but o- and p-substituted compounds tend to have a stronger inhibitory effect on thromboxane synthetase compared with m-substituted compounds.

In the imidazole derivatives of the formula (I) above of this invention, both of ester compounds and free acid compounds possess a strong inhibitory effect on thromboxane synthetase.

Of the imidazole derivatives of the formula (I), the compounds having an alkyl group as a branched chain, also are as strong on the inhibitory effect as the corresponding compounds having a linear alkylene or alkenylene group.

Furthermore, no significant difference is found in the inhibitory effect between the alkylene compounds and alkenylene compounds, and the imidazole derivatives of the formula (I) having one or more unsaturated bonds, involve the isomers, and those isomers may be employed for this invention.

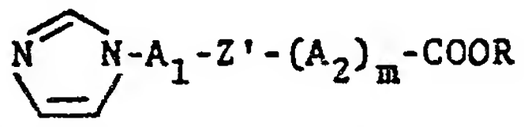
In the compounds wherein Y is bonded to A_1, preferred compounds include compounds wherein A_1 is methylene or ethylene group and A_2 is an alkylene group having two and below linear carbon atoms, or m is 0, such as p-[β-(1-imidazolyl)ethoxy]cinnamic acid, 3-[p-[β-(1-imidazolyl)ethoxy]-phenyl]propionic acid, p-[β-(1-imidazolyl)ethoxy]benzoic acid, p-[β-(1-imidazolyl)ethylamino]benzoic acid, p-[γ-(1-imidazolyl)propoxy]benzoic acid and alkyl esters of these acids. In the above preferred compounds, more preferred compounds include compounds wherein Z has an oxygen atom or a nitrogen atom and A_1 is a methylene group and m is 0. That is, p-[β-(1-imidazolyl)ethoxy]benzoic acid and -[β-(1-imidazolyl)ethylamino]benzoic acid are more preferred.

In the compounds wherein Y is bonded to A_2 or COOR group (in case of m being 0), preferred compounds include compounds wherein A_1 is methylene group, m is 0 or A_2 is an alkylene group having three and less carbon atoms, such as o-(1-imidazolylmethyl)phenoxyacetic acid, m-(1-imidazolylmethyl)phenoxyacetic acid, p-(1-imidazolylmethyl)phenoxyacetic acid, 2-[o-(1-imidazolylmethyl)phenoxy]propionic acid, 2-[p-(1-imidazolylmethyl)phenoxy]propionic acid, α-[p-(1-imidazolylmethyl)phenoxy]isobutyric acid, α-[p-(1-imidazolylmethyl)phenylthio]isobutyric acid and alkyl esters of these acids.

In these preferred compounds, more preferred compounds include compounds wherein Z has an oxygen atom and A_1 is methylene group, and m is 0 or A_2 is an alkylene group having three and less carbon atoms. That is, p-(1-imidazolylmethyl)phenoxyacetic acid, ethyl 2-[o-(1-imidazolylmethyl)phenoxy]propionate, 2-[p-(1-imidazolylmethyl)phenoxy]propionate and α-[p-(1-imidazolylmethyl)phenoxy]isobutyric acid are more preferred.

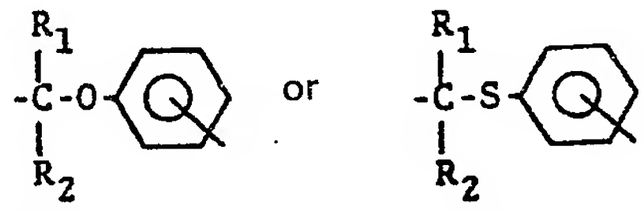
The imidazole derivatives of the formula (I) of this invention can be prepared by the following procedures.

Of the imidazole derivatives of the formula (I), for example, the compounds of the formula (Ia):



(Ia)

wherein A_1, A_2 and m have the same meanings as given above, and Z′ is



wherein R_1 and R_2 have the same meanings as given above, and the terminal carbon atom bonded to the hetero atom of Z′ may be bonded to A_1 or A_2 or COOR group (in case of m being 0), can be prepared by reacting imidazole of the formula (II):

(II)

with a compound of the formula (III):

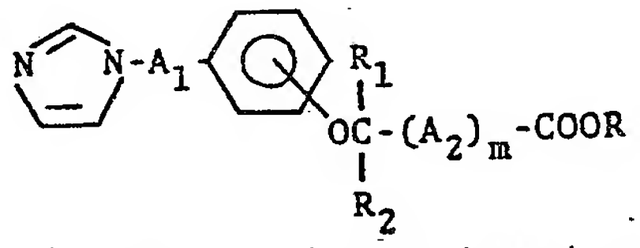
$$X—A_1—Z'—(A_2)_m—COOR_3 \quad \text{(III)}$$

wherein A_1, A_2, Z′ and m have the same meanings as given above, and X is an acid residual group, and

R_3 is an alkyl group, and then, if desired, hydrolyzing the resulting product to form a compound wherein R is a hydrogen atom.

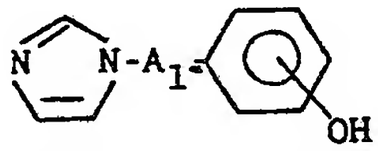
The above-described process is well known in this art, and can easily be carried out according to the procedure described in literature. That is, the N-alkylation described above in the reaction of imidazole of the formula (II) with a compound of the formula (III) can easily be carried out by dissolving or suspending a basic substance such as sodium carbonate, potassium carbonate, sodium hydride, sodium hydroxide, potassium hydroxide, a sodium alkoxide such as sodium methoxide, sodium ethoxide and the like, diisopropylethylamine, pyridine, triethylamine, etc., in an inert organic solvent, e.g., benzene, tetrahydrofuran, dioxane, toluene, xylene, acetonitrile, N,N-dimethylformamide, ethanol, butanol, etc., and to the solution or suspension, adding imidazole in an equimolar amount to the basic substance, and then heating the mixture to about room temperature to about 150°C for about 10 minutes to about 20 hours, subsequently, adding a solution of the compound of the formula (III) in a proportion of about 1 to 0.9 mol per mol of imidazole in an inert organic solvent such as those described above to the reaction mixture, and heating the resulting mixture to about 20 to 150°C for about 10 minutes to about 20 hours. The reaction mixture is concentrated under reduced pressure, and the residue is recrystallized or column chromatographed to obtain the desired product. If desired, the resulting product is hydrolyzed in the usual manner in an aqueous solution of an alkali to obtain the acid compound. In this process, instead of using the basic substance, the reaction can be carried out by using imidazole in an excess amount, e.g., more than twice molar amounts, of the compound of the formula (III) above. The reaction can also be carried out in the absence of any solvent, and can be carried out in the presence of a crown ether or a phase transfer catalyst such as tetrabutyl ammonium bromide, etc.

Of the imidazole derivatives of the formula (Ia), the compounds of the formula (Ia'):



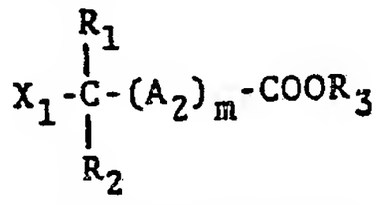
(Ia')

wherein A_1, A_2, R, R_1, R_2 and m have the same meanings as given above, can also be prepared by reacting a compound of the formula (IV):



(IV)

wherein A1 has the same meanings as given above, with a compound of the formula (V):



(V)

wherein A_2, R_1, R_2 and R_3 have the same meanings as given above, and X_1 is an acid residual group, and then, if desired, hydrolyzing the resulting compound to form a compound wherein R is a hydrogen atom.

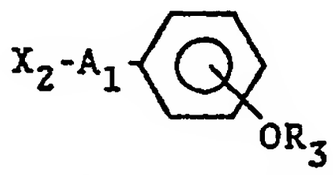
This reaction is also well known in this art, and can be carried out according to the procedure described in literature. That is, the O-alkylation described above in the reaction of a compound of the formula (IV) with a compound of the formula (V) can easily be carried out by dissolving or suspending a basic substance such as sodium carbonate, potassium carbonate, sodium hydride, sodium hydroxide, potassium hydroxide, a sodium alkoxide such as sodium methoxide and the like, diisopropylethylamine, pyridine, triethylamine, etc., in an inert organic solvent, e.g., benzene, tetrahydrofuran, dioxane, toluene, xylene, N,N-dimethylformamide, ethanol, butanol, etc., and to the solution or suspension, adding a compound of the formula (IV) in an equimolar amount to the basic substance, and then heating the mixture to about 40 to about 150°C for about 10 minutes to about 2 hours, subsequently, adding a solution of the compound of the formula (V) in a proportion of about 1 to 0.9 mol per mol of the compound of the formula (IV) in an inert organic solvent such as those described above to the reaction mixture, and heating the resulting mixture to about 50 to about 150°C for about 30 minutes to about 8 hours. The reaction mixture is concentrated under reduced pressure, and the residue is recrystallized or column chromatographed to obtain the desired product. If desired, the resulting product is hydrolyzed in the usual manner in an aqueous solution of an alkali to obtain the acid compound.

In the above processes, the imidazole of the formula (II), the compound of the formula (II), the compound of the formula (V) used as starting materials are well known and can easily be prepared according to the methods disclosed in literatures.

The compound of the formula (IV) is a new compound and can be prepared by reacting imidazole of the formula (II):

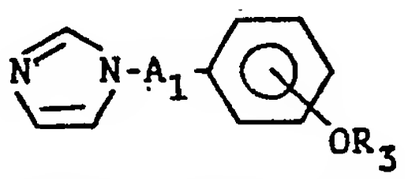
(II)

with a compound of the formula (IV):



(VI)

wherein A_1 and R_3 have the same meanings as given above, and X_2 is an acid residual group, to obtain a compound of the formula (VII):

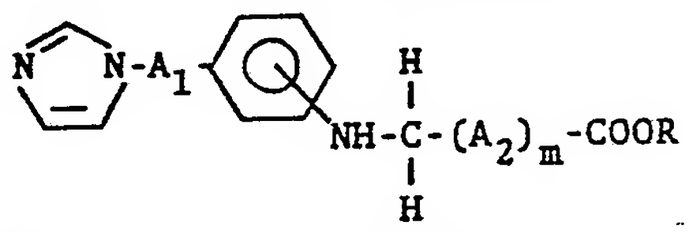


(VII)

wherein A_1 and R_3 have the same meanings as given above, and then dealkylating the resulting product to obtain a compound of the formula (IV).

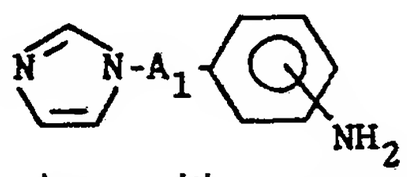
The above-described process for the production of a compound of the formula (IV) can be carried out by suspending a basic substance such as sodium carbonate, potassium carbonate, sodium hydride, sodium hydroxide, potassium hydroxide, a sodium alkoxide such as sodium methoxide, sodium ethoxide and the like, diisopropylamine, pyridine, triethylamine, etc., in an inert organic solvent, e.g., benzene, tetrahydrofuran, dioxane, toluene, xylene, acetonitrile, N,N-dimethylformamide, ethanol, etc., and adding imidazole in an equimolar amount to the basic substance to the suspension, and heating the mixture to about room temperature to about 200°C for about 10 minutes to about 20 hours, subsequently, adding a compound of the formula (VI) in a proportion of about 1 to 0.9 mol per mol of imidazole to the reaction mixture, then heating the resulting mixture to about 20 to about 150°C for about 10 minutes to about 20 hours, concentrating the resulting reaction mixture, and then recrystallizing or column chromatographing the residue to obtain a compound of the formula (VII), and then dealkylating the compound thus-obtained using an acid such as hydrobromic acid, etc., according to the usual manner to obtain the desired compound.

Of the imidazole derivatives of the formula (I), the compounds of the formula (Ib):



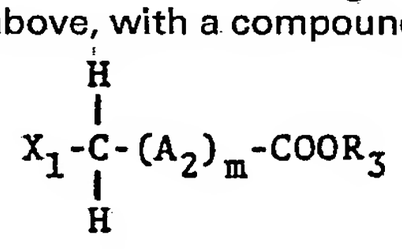
(Ib)

wherein A_1, A_2, R and m have the same meanings as given above, can be prepared by reacting a compound of the formula (VIII):



(VIII)

wherein A_1 has the same meanings as given above, with a compound of the formula (V'):



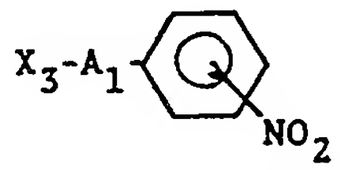
(V')

wherein X_1, A_2, R_3 and m have the same meanings as given above, and, if desired, hydrolyzing the resulting compound to form a compound wherein R is a hydrogen atom.

The above-described process for the production of a compound of the formula (Ib) can be carried out according to the procedure known per se. That is, a solution of a compound of the formula (VIII) and formic acid in an inert organic solvent such as toluene, xylene, etc., is heated under reflux for about 3 hours to 8 hours while removing the water formed. The reaction mixture is concentrated under reduced pressure, and the residue is recrystallized or column chromatographed to obtain an N-formylaniline compound. Then, the resulting compound is added to a suspension or a solution of a basic substance such as sodium hydride, a sodium alkoxide such as sodium methoxide, sodium ethoxide and the like, etc., in an equimolar amount to the N-formylaniline compound, in an inert organic solvent, e.g., benzene, dioxane, toluene, xylene, tetrahydrofuran, N,N-dimethylformamide, etc., and the mixture is heated to about 40 to about 150°C for 10 minutes to about 3 hours. A solution of a compound of the formula (V') in an inert organic solvent such as described above is added to the reaction mixture, and the resulting mixture is heated to about 50 to about 150°C for about 8 hours to about 20 hours. The reaction mixture is concentrated under reduced pressure, and the residue is purified by recrystallization or column chromatography. The compound thus-obtained is converted to the desired product by treating in the usual manner to remove the formyl group. In this process, the compound of the formula (V') used as starting material is a known compound and can be prepared according to the method disclosed in literature. The compound of the formula (VIII) used as starting material is a new compound and can be prepared by reacting imidazole of the formula (II):

(II)

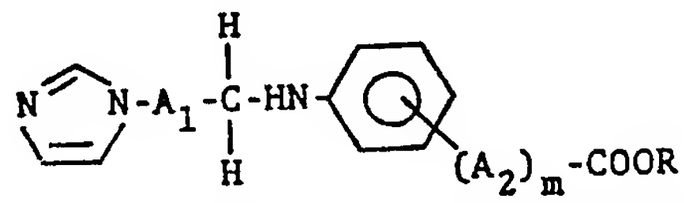
with a compound of the formula (IX):



(IX)

wherein A_1 has the same meanings as given above and X_3 is an acid residual group, according to the reaction of imidazole with a compound of the formula (VI), and then hydrogenating the resulting compound using a catalyst such as palladium-charcoal, etc., under a pressure of 1 to 5 atms.

Of the imidazole derivatives of the formula (I), the compound of the formula (Ic):

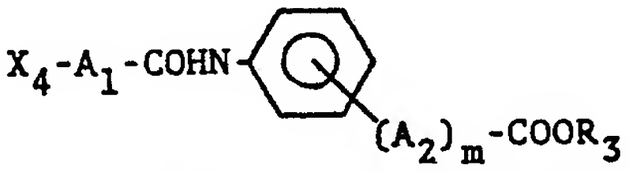


(Ic)

wherein A_1, A_2, R and m have the same meanings as given above, can be prepared by reacting imidazole of the formula (II):

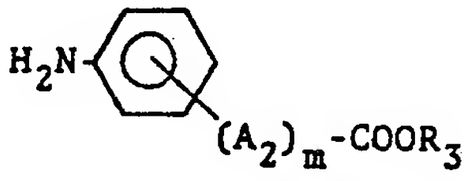
(II)

with a compound of the formula (X):



(X)

wherein A_1, A_2, m and R_3 have the same meanings as given above, and X_4 is an acid residual group, and then reducing the resulting product using a reducing agent such as sodium acetoxyborohydride, etc., to obtain a compound of the formula (Ic). This reaction is also well known, and can be easily carried out by the following procedures. That is, to a solution of a basic substance such as sodium carbonate, potassium carbonate, sodium hydride, sodium hydroxide, potassium hydroxide, a sodium alkoxide such as sodium methoxide, sodium ethoxide and the like, diisopropylethylamine, pyridine, triethylamine, etc., in an inert organic solvent, e.g., benzene, tetrahydrofuran, dioxane, toluene, xylene, N,N-dimethylformamide, ethyl alcohol, etc., is added imidazole in an equimolar amount to the basic substance, and the mixture is heated to room temperature to about 150°C for about 10 minutes to about 3 hours. A solution of a compound of the formula (X) in a proportion of 1 to 0.9 mol per mol of the imidazole in an inert organic solvent such as those described above is then added to the reaction mixture, and the resulting mixture is heated to about 50 to about 150°C for about 1 hour to about 5 hours. The reaction mixture is concentrated under reduced pressure, and the residue is purified by distillation or column chromatography to obtain an imidazolyl-amide compound. Then, the resulting compound is dissolved in an inert organic solvent such as tetrahydrofuran, diethyl ether, benzene, etc., and to solution is added an adequate amount of a reducing agent such as sodium acetoxyborohydride, etc., and then the mixture is heated to about 30 to about 150°C for about 1 hour to about 5 hours. The reaction mixture is concentrated under reduced pressure, and the residue is purified by distillation or column chromatography to a compound of the formula (Ic). In this process, the compound of the formula (X) used as starting material is a new compound and can be prepared by reacting a compound of the formula (XI):



(XI)

wherein A_2, R_3 and m have the same meanings as given above, with a compound of the formula (XII):

$$X_4—A_1—COOH \qquad \text{(XII)}$$

wherein A_1 and X_4 have the same meanings as given above, or with a reactive functional derivatives of the compound of the formula (XII), according to the usual method.

In this invention, a compound of the formula (I) wherein A_1 and/or A_2 are alkenylene groups can also be converted to the compound having an alkylene group except for the compound having sulfur atom by catalytically hydrogenating in the presence of a catalyst such as palladium-charcoal, platinum dioxide, etc., under hydrogen gas atmosphere.

The compounds of the formula (I) of this invention having a free carboxyl group or a free amine

group can be converted according to the usual methods to pharmaceutically acceptable salts thereof. For example, the free-form compound of the formula (I) is dissolved in a solvent, e.g., an alcohol, water, etc., an adequate amount of hydrochloric acid or sodium hydroxide is added to the solution, the mixture is stirred at room temperature for an adequate period of time, the solvent is then distilled off, and the residue is recrystallized to obtain the salt of compound of the formula (I). Suitable examples of such pharmaceutically acceptable salts include in addition to the hydrochloric acid salt, the sulfuric acid salt, the nitric acid salt, the phosphoric acid salt, the sulfonic acid salt, the benzoic acid salt, the succinic acid salt, the tartaric acid salt, the citric acid salt, etc. On the other hand, as examples of such pharmaceutically acceptable base additional salts, in addition to the sodium salt, there are the potassium salt, the calcium salt, the magnesium salt, etc.

In the case of the salts of the compounds of the formula (I), the salt form of the compounds can be converted according to the usual methods to the free form of the compound thereof. For example, the salt form of the compound of the formula (I) is dissolved in water, then an adequate amount of hydrochloric acid or sodium hydroxide is added to solution, and the mixture is stirred at room temperature for an adequate period of time, water is removed, and the residue is distilled under reduced pressure or recrystallized from a solvent to obtain the desired compound.

Acid or base addition salts of the compounds of this invention have as high an inhibitory effect on thromboxane synthetase as the corresponding compounds having a free amino group or an acid group.

The imidazole derivatives of this invention possess a strong inhibitory effect on thromboxane synthetase, for example, 4-(1-imidazolylmethyl)phenoxyacetic acid hydrochloride produce a 50% inhibition for thromboxane synthetase from human or bovine platelet microsomes at the molar concentrations 4×10^{-8}, and are useful as therapeutically active agents for the treatment of inflammation, hypertension, thrombus, cerebral apoplexy and asthma.

The imidazole derivatives of the formula (I) and the pharmaceutically acceptable salts thereof of this invention can be administered to mammals including humans by oral, intravenous, intramuscular or intrarectal administration, and for such administration they can be formulated into pharmaceutical compositions together with conventional pharmaceutically acceptable carriers.

The compounds can be administered in various forms according to the purposed therapy. Typical dosage forms which can be used are tablets, pills, powders, liquid preparations, suspensions, emulsions, granules, capsules, suppositories and injectable preparations.

In molding the pharmaceutical composition into a tablet form, a wide variety of conventional carriers known in this art can be used. Examples of suitable carriers are excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin and talc, binders such as gum arabic powder, tragacanth powder, and ethanol, and disintegrants such as laminaria and agar. The tablets, if desired, can be coated to make sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or tablets coated with two or more layers.

When the pharmaceutical composition is formulated into an injectable preparation, the resulting solution and suspension are preferably sterilized, and are isotonic with respect to the blood. In formulating the pharmaceutical composition into the form of a solution or suspension, any types of diluents customarily used in the art can be used. Examples of suitable diluents are water, ethyl alcohol, propylene glycol, ethoxyate isostearyl alcohol, polyoxyethylene sorbitol, and sorbitan esters. Sodium chloride, glucose or glycerol may be incorporated into a therapeutic agent in an amount sufficient to prepare an isotonic solution. The therapeutic agent may further contain ordinary dissolving aids, buffers, pain-alleviating agents, and preservatives, and optionally, coloring agents, perfumes, flavors, sweeteners and other drugs.

The dosage of the compound of this invention can be about 1 mg to 1,000 mg/body by oral administration, or about 0.1 mg to 100 mg/body by parenteral administration per day for adult human in multiple doses depending upon the disease which is being treated.

This invention is further illustrated in more detail by way of the following examples wherein the melting point or the boiling point of the product obtained are uncorrected. Unless otherwise indicated, all parts, percents, ratios and the like are by weight.

COMPARATIVE EXAMPLE 1

p-(1-Imidazolylmethyl)phenol hydrobromide

To a suspension of 5.21 g of 50% sodium hydride in 100 ml of dry dimethylformamide was added slowly 7.39 g of imidazole at room temperature, and the mixture was stirred for 20 minutes. A solution of 20 g of p-methoxybenzyl chloride in 30 ml of dry dimethylformamide was added to the mixture at room temperature over a period of 1 hour, and then the reaction mixture was stirred for 18 hours at 50°C. After removal of the solvent under reduced pressure, 100 ml of dichloromethane was added to the residual oil and the mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual solid was recrystallized from diethyl ether-ligroin to give 14.7 g of p-(1-imidazolylmethyl)anisole as colorless platelets. Then a solution of 14.7 g of p-(1-imidazolylmethyl)anisole in 50 ml of 47% hydrobromic acid was refluxed for 3 hours. After

concentration under reduced pressure, the residual solid was recrystallized from ethanol-diethyl ether to give 18.4 g of p-(1-imidazolylmethyl)phenol hydrobromide as colorless platelets. M.P.: 189—190°C.
NMR Spectrum (DMSO—D_6):
δ 5.49 (s, 2H), 6.97 (d, 2H), 7.49 (d, 2H), 7.88 (t, 1H), 7.99 (t, 1H), and 9.49 (br-s, 1H)
Elemental Analysis as $C_{10}H_{10}N_2O \cdot HBr$:
Calcd. C, 47.08; H, 4.35; N, 10.98
Found C, 47.12; H, 4.22; N, 10.92

REFERENCE EXAMPLE 2
p-(1-Imidazolylmethyl)aniline

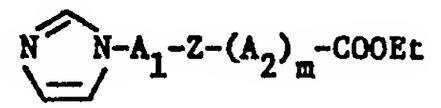
A mixture of 13.6 g of imidazole, 43.2 g of p-bromomethylnitrobenzene and 55.2 g of anhydrous potassium carbonate in 300 ml of dry toluene was refluxed for 18 hours. After concentration under reduced pressure, 200 ml of dichloromethane was added to the residue and insoluble salts were filtered off. The filtrate was evaporated and the residue was chromatographed on silica gel using dichloromethane-ethanol (20:1 by volume) to give 27.9 g of p-(1-imidazolylmethyl)nitrobenzene as pale yellow platelets. Then, a solution of 2.0 g of this product in 50 ml of ethanol was hydrogenated over 0.2 g of palladium on carbon at room temperature under a hydrogen pressure of 4 atms. After filtration and evaporation, the residual solid was recrystallized from ethanol-diethyl ether-petroleum ether to give 1.4 g of p-(1-imidazolylmethyl)aniline as colorless needles. M.P.: 134—137°C.
IR-Absorption Spectrum (KBr):
νNH 3300 cm^{-1} and 3450 cm^{-1}
NMR Spectrum ($CDCl_3$):
δ 3.96 (br, 2H), 5.01 (s, 2H), 6.70 (d, 2H), 6.95 (t, 1H), 7.04 (d, 2H), 7.12 (m, 1H), and 7.59 (br-s, 1H)
Elemental Analysis as $C_{10}H_{11}N_3$:
Calcd. C, 69.34; H, 6.40; N, 24.26
Found C, 69.23; H, 6.41; N, 24.12

EXAMPLE 1
Ethyl 2-[o-(1-imidazolylmethyl)phenoxy]propionate

To a suspension of 5.7 g of 50% sodium hydride in 200 ml of dry dimethylformamide was added slowly 8.0 g of imidazole at room temperature, and then the mixture was stirred for 30 minutes. A solution of 34.1 g of ethyl 2-(o-bromomethylphenoxy)propionate in 50 ml of dry dimethylformamide was added to the mixture at room temperature over a period of 1 hour, and then the reaction mixture was stirred at the same temperature for 1 hour. After removal of the solvent under vacuum, 150 ml of dichloromethane was added to the residual oil and the solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual oil was chromatographed on silica gel using dichloromethane-ethanol (20:1 by volume) to give 15 g of ethyl 2-[o-(1-imidazolylmethyl)phenoxy]propionate as colorless needles. M.P.: 84—85°C.
IR-Absorption Spectrum (KBr):
νCO 1740 cm^{-1}
NMR Spectrum ($CDCl_3$):
δ 1.24 (t, 3H), 1.64 (d, 3H), 4.27 (q, 2H), 4.90 (q, 1H), 5.26 (s, 2H), 6.8—7.54 (m, 6H), and 7.69 (br-s, 1H)
Elemental Analysis as $C_{15}H_{18}O_3N_2$:
Calcd. C, 65.67; H, 6.61; N, 10.21
Found C, 65.68; H, 6.75; N, 10.01
The following compounds were prepared in a similar manner to the procedure described above.

TABLE 1

+ $X–A_1–Z–(A_2)_m–COOEt$ →



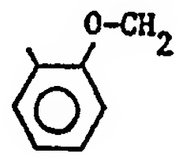
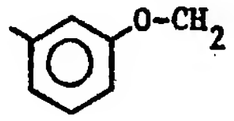
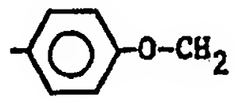
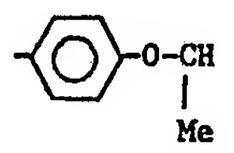
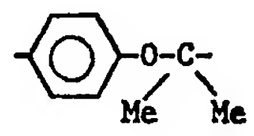
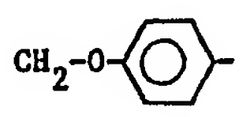
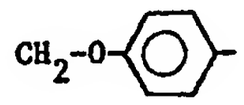
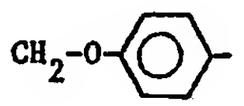
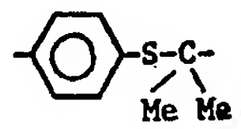
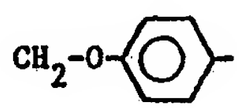
X	A_1	m	A_2	Z	Yield (%)	M.P. (°C)	IR (cm^{-1})	NMR ($CDCl_3$) δ
Br	CH_2	0	–		36	61–62	(KBr) νCO 1740	1.32(t,3H), 4.36(q,2H), 4.71(s,2H), 5.26(s,2H) 6.8–7.5(m,6H), and 7.72(br-s,1H).
Br	CH_2	0	–		38	oil	(neat) νCO 1755	1.26(t,3H), 4.24(q,2H), 4.55(s,2H), 5.04(s,2H), and 6.6–7.5(m,7H).
Br	CH_2	0	–		55	oil	(neat) νCO 1750	1.27(t,3H), 4.24(q,2H), 4.58(s,2H), 5.00)s,2H), 6.7–7.1(m,6H), and 7.45(br-s,1H).
Br	CH_2	0	–		45	oil	(neat) νCO 1740	1.21(t,3H), 1.59(d,3H), 4.19(q,2H), 4.70(q,1H), 4.96(s,2H), 6.7–7.1(m,6H), and 7.44(br-s,1H).
Br	CH_2	0	–		60	oil	(neat) νCO 1725	1.25(t,3H), 1.61(s,6H), 4.29(q,2H), 5.10(s,2H), 6.8–7.3(m,6H), and 7.59(br-s,1H).
Br	CH_2	0	–		58	96–97	(KBr) νCO 1700	1.40(t,3H), 4.2–4.6(m,6H), 6.99(d,2H), 7.17(br-s,2H), 7.72(br-s,1H), and 8.12(d,2H).

TABLE 1 (cont'd)

X	A_1	m	A_2	Z	Yield (%)	M.P. (°C)	IR (cm^{-1})	NMR ($CDCl_3$) δ
Br	CH_2	1	CH=CH		55	89–90	(KBr) νCO 1705 νC=C 1635	1.30(t,3H), 4.1–4.4(m,6H), 6.24(d,1H), 6.79(d,2H), 6.95–7.05(m,2H), and 7.3–7.65(m,4H).
Br	CH_2	1	$(CH_2)_2$		60	oil	(neat) νCO 1730	1.20(t,3H), 2.45–2.65(m,2H), 2.80–3.0(m,2H), 4.10(q,2H), 4.05–4.40(m,4H), 6.74(d,2H), 6.95–7.05(m,2H), 7.04(d,2H), and 7.52(br-s,1H).
Br	CH_2	0	–		60	oil	(neat) νCO 1720	1.21(t,3H), 1.48(s,6H), 4.16(q,2H), 5.19(s,2H), 6.97(br-s,1H), 7.05–7.25(m,3H), and 7.45–7.65 (m,3H).
Br	$(CH_2)_2$	0	–		60	oil	(neat) νCO 1700	1.38(t,3H), 2.25(m,2H), 3.98(t,2H), 4.20(t,2H), 4.36(q,2H), 6.8–7.1(m,4H), 7.50(br-s,1H), and 8.00(d,2H).

EXAMPLE 2

Ethyl 4-[p-(1-imidazolylmethyl)phenoxy]butyrate

5.0 g of p-(1-imidazolylmethyl)phenol hydrobromide prepared as described in Reference Example 1 was added slowly to a suspension of 1.88 g of 50% sodium hydride in 100 ml of dry dimethylformamide at room temperature, and then the mixture was warmed to 45°C. A solution of 3.82 g of ethyl 4-bromobutyrate in 30 ml of dry dimethylformamide was added to the mixture over a period of 30 minutes at 45°C, and then the reaction mixture was stirred for 17 hours at the same temperature. After removal of the solvent, the residual oil was diluted with 100 ml of dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel using dichloromethane-ethanol (20:1 by volume) to give 3.43 g of ethyl 4-p-(1-imidazolylmethyl)phenoxybutyrate as a colorless oil.

IR-Absorption Spectrum (neat):

νCO 1725 cm^{-1}

NMR Spectrum ($CDCl_3$):

δ 1.26 (t, 3H), 2.18 (m, 2H), 2.45—2.65 (m, 2H), 4.05 (t, 2H), 4.20 (q, 2H), 5.09 (s, 2H), 6.85—7.3 (m, 6H), and 7.61 (br-s, 1H)

Elemental Analysis as $C_{16}H_{20}O_3R_2$:

Calcd. C, 66.64; H, 6.99; N, 9.72

Found C, 66.38; H, 7.20; N, 9.43

EXAMPLE 3

Ethyl p-[β-(1-imidazolyl)ethylamino]benzoic acid hydrochloride

To a suspension of 2.4 g of 50% sodium hydride in 100 ml of dry dimethylformamide was added slowly 3.4 g of imidazole at room temperature, and the mixture was heated to 80°C. A solution of 12.1 g of ethyl p-chloroacetylaminobenzoate in 45 ml of dry dimethylformamide was added to the mixture over a period of 30 minutes at 80°C, and then the reaction mixture was heated at 100°C for 1.5 hours. After removal of the solvent under reduced pressure, the residue was dissolved in chloroform and washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual solid was recrystallized from ethanol-n-hexane to give 10.5 g of ethyl p-(1-imidazolyl)acetylaminobenzoate as colorless needles. M.P.: 185—187°C.

IR-Absorption Spectrum (KBr):

νCO 1700 cm^{-1}

NMR Spectrum (DMSOD—):

δ 1.29 (t, 3H), 4.29 (q, 2H), 4.93 (s, 2H), 6.89 (br-s, 1H), 7.13 (br-s, 1H), 7.62 (br-s, 1H), 7.70 (d, 2H), 7.91 (d, 2H), and 10.59 (br-s, 1H)

Elemental Analysis as $C_{14}H_{15}O_3N_3$:

Calcd. C, 61.53; H, 5.53; N, 15.38

Found C, 61.52; H, 5.59; N, 15.26

Then, a suspension of 7.2 g of ethyl p-(1-imidazolyl)acetylaminobenzoate and 12.7 g of sodium acetoxyborohydride in 200 ml of dry tetrahydrofuran was stirred at room temperature for 1 hour and then refluxed for 5 hours. After evaporation under reduced pressure, 50 ml of water was added in small portions to the residue to decompose the excess of sodium acetoxyborohydride and the complex, and then the aqueous solution was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and saturated with dry hydrogen chloride gas at room temperature, followed by allowing to stand for 1 hour. Then, the solvent was evaporated and the residual solid was recrystallized from ethanol-diethyl ether to give 4.5 g of ethyl p-[β-(1-imidazolyl)ethylamino]benzoate hydrochloride as colorless leaflets. M.P.: 166—168°C.

IR—Absorption Spectrum (KBr):

νCO 1750 cm^{-1}

νNH 3280 cm^{-1}

NMR Spectrum (DMSO—D_6):

δ 1.27 (t, 3H), 3.64 (t, 2H), 4.22 (q, 2H), 4.46 (t, 2H), 5.4—5.9 (br, 2H), 6.65 (d, 2H), 7.63 (br-s, 1H), 7.65 (d, 2H), 7.84 (br-s, 1H), and 9.26 (br-s, 1H)

Elemental Analysis as $C_{14}H_{17}O_2N_3 \cdot HCl \cdot \frac{1}{4}H_2O$:

Calcd. C, 56.00; H, 6.21; N, 14.00

Found C, 55.91; H, 6.17; N, 14.05

Then a solution of 1.0 g of ethyl p-[β-(1-imidazolyl)ethylamino]benzoate hydrochloride and 1.0 g of sodium hydroxide in 30 ml of methanol-water (1:2 by volume) was stirred for 2.5 hours at room temperature. After concentration under reduced pressure, the residue was acidified with 6N hydrochloric acid to pH 1, and then concentrated under reduced pressure. To the residue was added 20 ml of tert-butanol and evaporated under reduced pressure to remove the excess of hydrochloric acid completely. The residual solid was dissolved in ethanol, the insoluble salts were filtered off, and then the filtrate was evaporated under reduced pressure. The residual solid was recrystallized from ethanol-diethyl ether to give 0.65 g of p-[β-(1-imidazolyl)ethylamino]benzoic acid hydrochloride as colorless needles. M.P.: 222 to 224°C (dec.).

IR-Absorption Spectrum (KBr):
νCO 1665 cm^{-1}
νNH 3240 cm^{-1}
NMR Spectrum (DMSO—D_6):
δ 3.5—3.8 (m, 2H), 4.25—4.6 (m, 2H), 6.62 (d, 2H), 7.4—8.0 (m, 5H), and 9.22 (br-s, 1H)
Elemental Analysis as $C_{12}H_{13}O_2N_3 \cdot HCl$:
Calcd. C, 53.83; H, 5.27; N, 15.70
Found C, 53.59; H, 5.46; N, 15.46

EXAMPLE 4
N-[p-(1-Imidazolylmethyl)phenyl]alanine ethyl ester dihydrochloride

In a 200 ml round-bottom flask is placed a solution of 8.0 g of p-(1-imidazolylmethyl)aniline prepared as described in Reference Example 3, and 30 ml of formic acid in 80 ml of toluene. The flask was fitted with a water separator, and the solution was refluxed for 4 hours. After concentration under reduced pressure, the residual solid was recrystallized from ethanol-diethyl ether to give 6.4 g of p-(1-imidazolylmethyl)-N-formylaniline as colorless prisms. M.P.: 121—123°C. To a suspension of 0.48 g of 50% sodium hydride in 50 ml of dry dimethylformamide was added 2.01 g of the formylaniline and mixture was heated to 100°C. A solution of 1.81 g of ethyl α-bromopropionate in 30 ml of dry dimethylformamide was added to the mixture and the reaction mixture was heated at 100°C for 16 hours. After removal of the solvent under reduced pressure, 50 ml of dichloromethane was added to the residue, and the solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel using dichloromethane-ethanol (20:1 by volume) to give 1.58 g of N-formyl-N-[p-(1-imidazolylmethyl)phenyl]alanine ethyl ester as a pale brown oil. Then, a solution of 1.58 g of the resulting ester and 5 ml of concentrated hydrochloric acid in 50 ml of ethanol was stirred for 40 hours at room temperature. After concentration under reduced pressure, the residual solid was recrystallized from ethanol-diethyl ether to give 1.18 g of N-[p-(1-imidazolylmethyl)phenyl]alanine ethyl ester dihydrochloride as pale yellow crystals. M.P.: 154—159°C.
IR-Absorption Spectrum (KBr):
νCO 1720 cm^{-1}
NMR Spectrum (DMSO—D_6):
δ 1.13 (t, 3H), 1.39 (d, 3H), 3.95—4.25 (m, 3H), 5.29 (s, 2H), 5.85—6.40 (br, 3H), 6.68 (d, 2H), 7.22 (d, 2H), 7.60 (m, 1H), 7.73 (m, 1H), and 9.33 (m, 1H)
Elemental Analysis as $C_{15}H_{19}O_2N_3 \cdot 2HCl$:
Calcd. C, 52.03; H, 6.11; N, 12.14
Found C, 51.77; H, 6.22; N, 12.15

EXAMPLE 5
N-[p-(1-Imidazolylmethyl)phenyl]glycine ethyl ester dihydrochloride

In the same procedure as described in Example 4, N-[p-(1-imidazolylmethyl)phenyl]glycine ethyl ester dihydrochloride was prepared from p-(1-imidazolylmethyl)aniline which was prepared as described in Reference Example 2, and ethyl bromoacetate. M.P.: 156—159°C (decomp.) (pale yellow prisms; recrystallized from ethanol-diethyl ether).
IR-Absorption Spectrum (KBr):
νCO 1740 cm^{-1}
NMR Spectrum (DMSO—D_6):
δ 1.17 (t, 3H), 3.92 (s, 2H), 4.10 (q, 2H), 5.27 (s, 2H), 6.62 (d, 2H), 7.0—8.0 (m, 7H), and 9.35 (m, 1H)
Elemental Analysis as $C_{14}H_{19}O_2N_3Cl_2$:
Calcd. C, 50.61; H, 5.76; N, 12.65
Found C, 50.33; H, 5.78; N, 12.51

EXAMPLE 6
p-(1-Imidazolylmethyl)phenoxyacetic acid hydrochloride monohydrate

A solution of 2.3 g of ethyl p-(1-imidazolylmethyl)phenoxyacetate prepared as described in Example 1, and 0.45 g of sodium hydroxide in 30 ml of methanol-water (1:2 by volume) was stirred for 30 minutes at room temperature. After concentration under reduced pressure, the residue was acidified with 6N hydrochloric acid to pH 11 and then concentrated under reduced pressure. To the residue was added 20 ml of tert-butanol, and evaporated under reduced pressure to remove the excess of hydrochloric acid completely. The residual solid was dissolved in ethanol and the insoluble salts were filtered off. The filtrate was evaporated and a small amount of water was added to the residue, and the resulting crystals were recrystallized from ethanol-diethyl ether-water (a small amount) to give 1.5 g of p-(1-imidazolylmethyl)phenoxyacetic acid hydrochloride monohydrate as colorless needles. M.P.: 92—96°C.

IR-Absorption Spectrum (KBr):

νCO 1755 cm^{-1}

NMR Spectrum (DMSO—D_6):

δ 4.67 (s, 2H), 5.40 (s, 2H), 5.6—6.1 (br, 4H), 6.88 (d, 2H), 7.38 (d, 2H), 7.60 (t, 1H), 7.75 (t, 1H), and 9.45 (br-s, 1H)

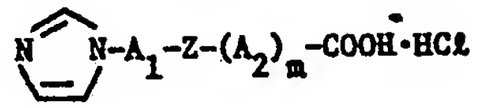
Elemental Analysis as $C_{12}H_{12}O_3N_2 \cdot HCl \cdot H_2O$:

Calcd. C, 50.27; H, 5.27; N, 9.73

Found C, 50.26; H, 5.18; N, 9.74

The following compounds were also prepared in a similar manner to the procedure described above.

TABLE 2



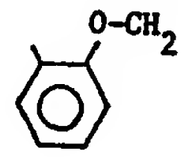
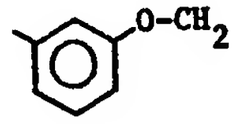
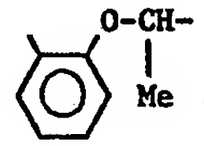
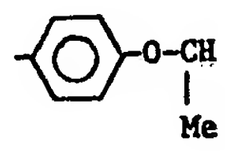
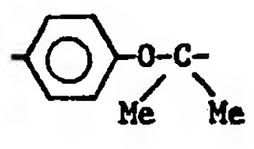
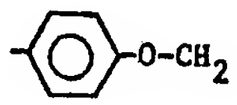
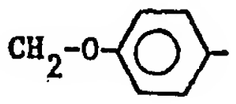
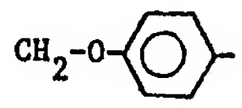
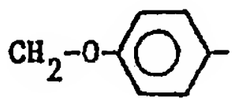
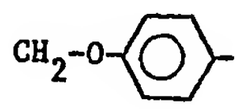
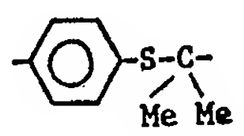
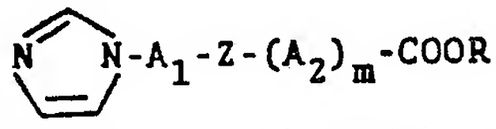
A_1	m	A_2	Z	Yield (%)	M.P. (°C)	IR (cm^{-1})	NMR (DMSO–D_6) δ
CH_2	0	–		82	167–169	(KBr) νCO 1745	4.89(s,2H), 5.52(s,2H), 7.0–7.7(m,4H), 7.75(t,1H), 7.92(t,1H), 9.35(br-s,1H), and 9.0–10.4(br,2H)
CH_2	0	–		75	173–175	(KBr) νCO 1740	4.67(s,2H), 5.41(s,2H), 6.75–7.40(m,4H), 7.63(t,1H), 7.79(t,1H), 9.45(br-s,1H), and 10.0–14.0 (br,2H)
CH_2	0	–		80	172–174	(KBr) νCO 1735	1.58(d,3H), 5.12(q,1H), 5.55(s,2H), 7.0–7.7(m, 4H), 7.76(br-s,1H), 7.85(br-s,1H), and 9.32(br-s, 1H)
CH_2	0	–		74	155–158	(KBr) νCO 1725	1.50(d,3H), 4.85(q,1H), 5,36(s,2H), 6.86(d,2H), 7.27(d,2H), 7.60(br-s,1H), 7.75(br-s,1H), and 9.35(br-s,1H)
CH_2	0	–		75	174–177	(KBr) νCO 1730	1.53(s,6H), 5.51(s,2H), 6.95(d,2H), 7.50(d,2H), 7.79(t,1H), 7.95(t,1H), 9.48(br-s,1H), and 12–13(br,2H)

TABLE 2 (cont'd)

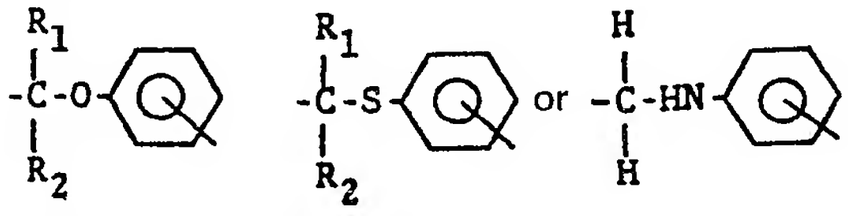
A_1	m	A_2	Z	Yield (%)	M.P. (°C)	IR (cm^{-1})	NMR (DMSO–D_6) δ
CH_2	1	$(CH_2)_2$		70	181–183	(KBr) νCO 1740	1.85–2.15(m,2H), 2.45(t,2H), 4.06(t,2H), 5.50(s,2H), 7.06(d,2H), 7.54(d,2H), 7.79(t,1H), 7.92(t,1H), and 9.50(m,1H)
CH_2	1	CH=CH		80	214–217	(KBr) νCO 1710 νC=C 1640	4.35–4.80(m,4H), 6.38(d,1H), 6.96(d,2H), 7.50(d,1H), 7.59(d,2H), 7.64(t,1H), 7.84(t,1H), 9.28(br-s,1H), and 9.5–12.5(br.2H)
CH_2	1	$(CH_2)_2$		75	184–186	(KBr) νCO 1720	2.35–2.65(m,2H), 2.65–2.95(m,2H), 4.25–4.50(m,2H), 4.50–4.80(m,2H), 6.80(d,2H), 7.08(d,2H), 7.63(t,1H), 7.81(t,1H), and 9.31(t,1H)
CH_2	0	–		90	230–235	(KBr) νCO 1675	4.4–4.6(m,2H), 4.6–4.8(m,2H), 7.01(d,2H), 7.67 t,1H), 7.85(d,2H), 7.86(t,1H), and 9.30(br-s,1H)
$(CH_2)_2$	0	–		80	192–193	(KBr) νCO 1700	2.35(m,2H), 4.12(t,2H), 4.45(t,2H), 6.95(d,2H), 7.65–8.0(m,4H), and 9.34(br-s,1H)
CH_2	0	–		75	169–171	(KBr) νCO 1710	1.38(s,6H), 5.61(s,2H), 7.53(s,4H), 7.81(m,1H), 7.95(m,1H), and 9.52(m,1H)

CLAIMS

1. An imidazole derivative of the formula:

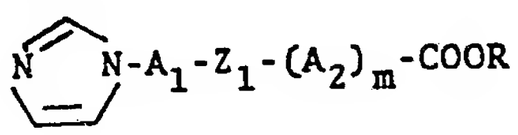


wherein R is a hydrogen atom or an alkyl group, A_1 and A_2, which may be the same or different, each is an alkylene group or an alkenylene group, m is 0 or 1, and Z is

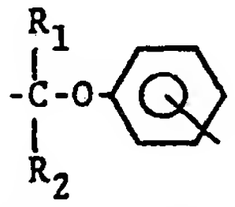


wherein R_1 and R_2, which may be the same or different, each is a hydrogen atom or an alkyl group, and the terminal carbon atom bonded to the hetero atom of Z may be bonded to A_1 or A_2 or COOR group (in case of m being 0); or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 of the formula:

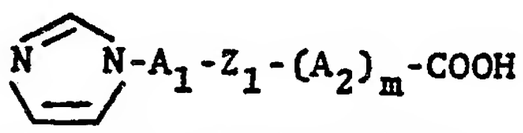


wherein Z_1 is



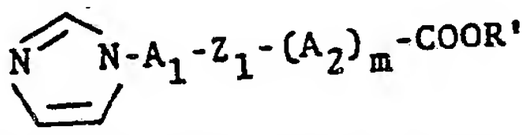
wherein R_1 and R_2 have the same meanings as given above, and the terminal carbon atom bonded to the hetero atom of Z may be bonded to A_1 or A_2 or COOR group (in case of m being 0), and A_1, A_2, m and R have the same meanings as given above; or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in Claim 2 of the formula:



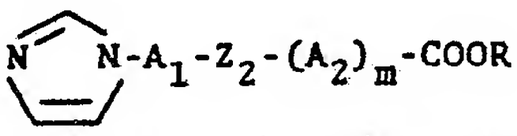
wherein A_1, A_2, Z_1 and m have the same meanings as given above.

4. A compound as claimed in Claim 2 of the formula:

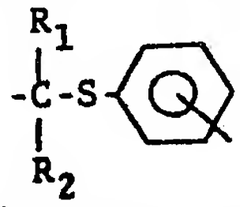


wherein A_1, A_2, Z_1 and m have the same meanings as given above and R′ is an alkyl group.

5. A compound as claimed in Claim 1 of the formula:

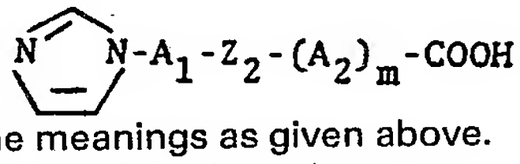


wherein A_1, A_2, m and R have the same meanings as given above and Z_2 is



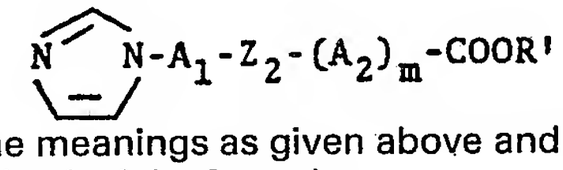
wherein R_1 and R_2 have the same meanings as given above, and the terminal carbon atom bonded to the hetero atom of Z may be bonded to A_1 or A_2 or COOR group (in case of m being 0).

6. A compound as claimed in Claim 5 of the formula:



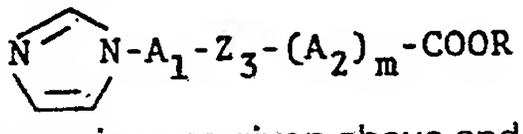
wherein A_1, A_2, Z_2 and m have the same meanings as given above.

7. A compound as claimed in Claim 5 of the formula:

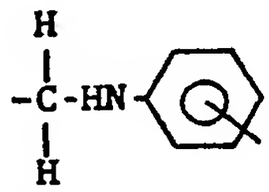


wherein A_1, A_2, Z_2 and m have the same meanings as given above and R′ is an alkyl group.

8. A compound as claimed in Claim 1 of the formula:

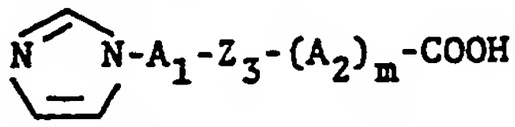


wherein A_1, A_2, m and R have the same meanings as given above and Z_3 is



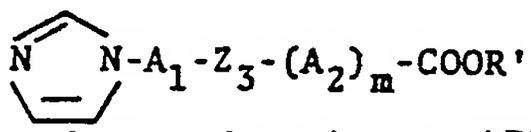
wherein the methylene group bonded to the amino group of Z may be bonded to either A_1 or A_2 or COOR group (in the case of m being 0); or a pharmaceutically acceptable salt thereof.

9. A compound as claimed in Claim 8 of the formula:



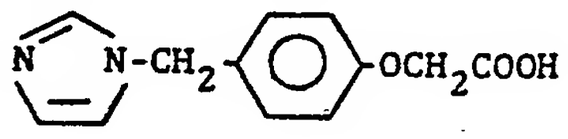
wherein A_1, A_2, Z_3 and m have the same meanings as given above.

10. A compound as claimed in Claim 8 of the formula:

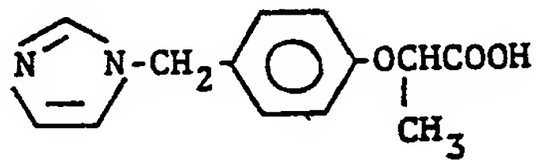


wherein A_1, A_2, Z_3 and m have the same meanings as given above and R′ is an alkyl group.

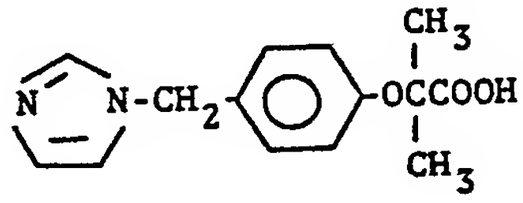
11. A compound as claimed in Claim 3 of the formula:



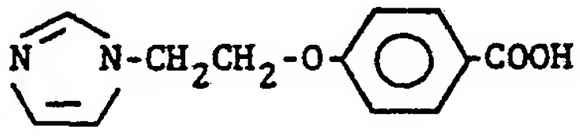
12. A compound as claimed in Claim 3 of the formula:



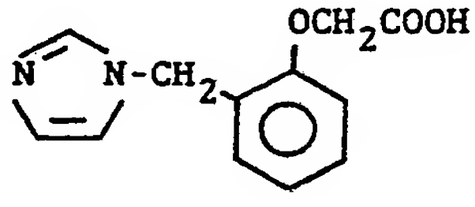
13. A compound as claimed in Claim 3 of the formula:



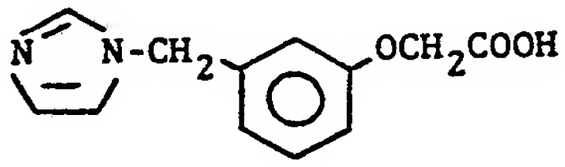
14. A compound as claimed in Claim 3 of the formula:



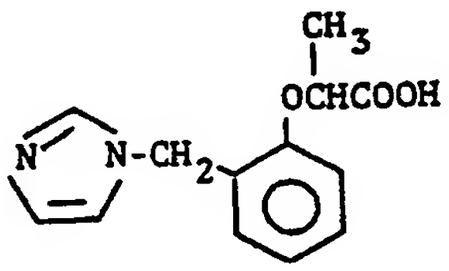
15. A compound as claimed in Claim 3 of the formula:



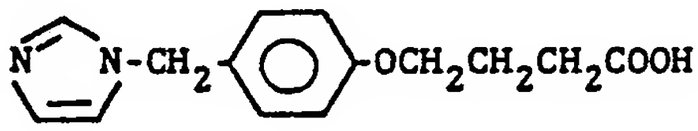
16. A compound as claimed in Claim 3 of the formula:



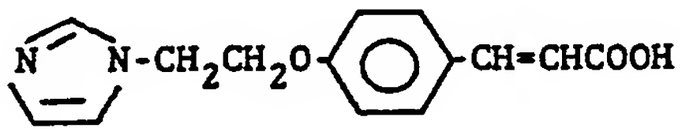
17. A compound as claimed in Claim 3 of the formula:



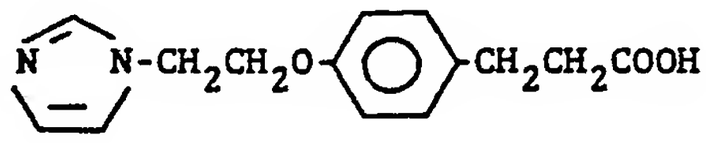
18. A compound as claimed in Claim 3 of the formula:

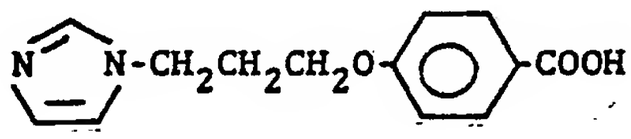


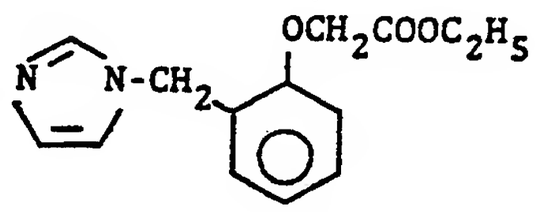
19. A compound as claimed in Claim 3 of the formula:

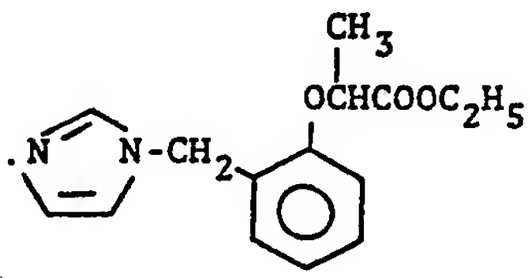


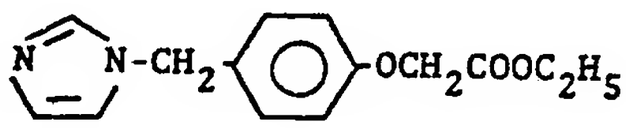
20. A compound as claimed in Claim 3 of the formula:

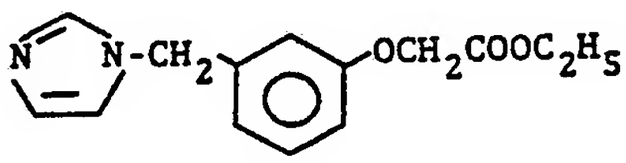


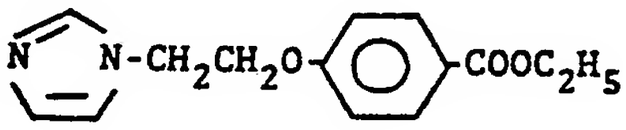
21. A compound as claimed in Claim 3 of the formula: 

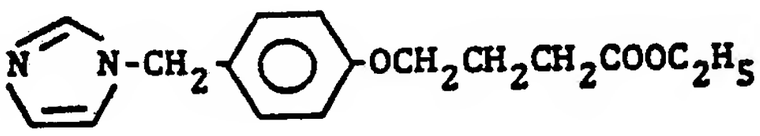
22. A compound as claimed in Claim 4 of the formula: 

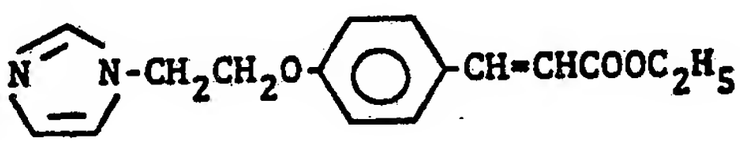
23. A compound as claimed in Claim 4 of the formula: 

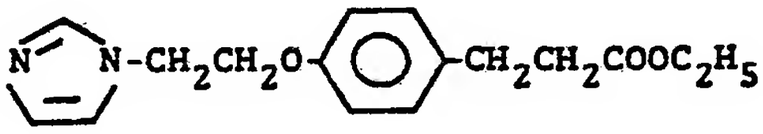
24. A compound as claimed in Claim 4 of the formula: 

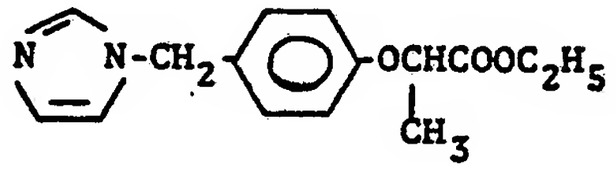
25. A compound as claimed in Claim 4 of the formula: 

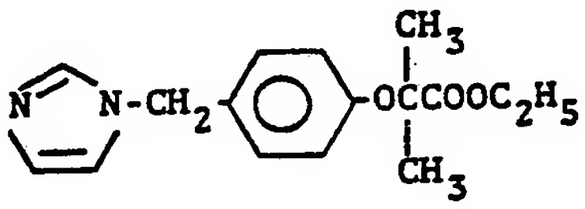
26. A compound as claimed in Claim 4 of the formula: 

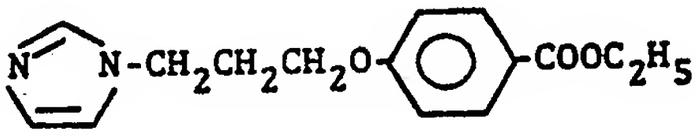
27. A compound as claimed in Claim 4 of the formula: 

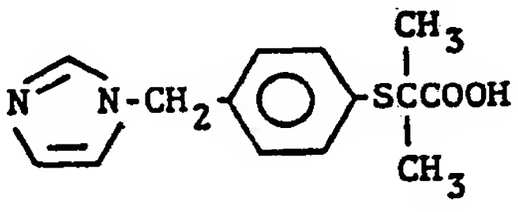
28. A compound as claimed in Claim 4 of the formula: 

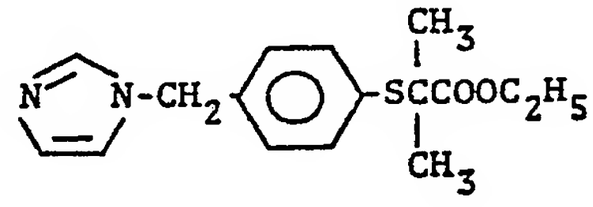
29. A compound as claimed in Claim 4 of the formula: 

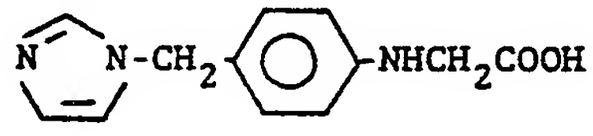
30. A compound as claimed in Claim 4 of the formula: 

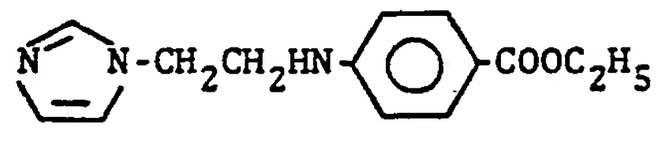
31. A compound as claimed in Claim 4 of the formula: 

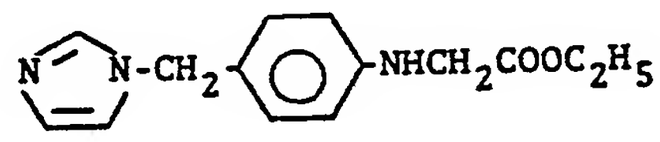
32. A compound as claimed in Claim 4 of the formula: 

33. A compound as claimed in Claim 6 of the formula: 

34. A compound as claimed in Claim 7 of the formula: 

35. A compound as claimed in Claim 9 of the formula: 

36. A compound as claimed in Claim 10 of the formula: 

37. A compound as claimed in Claim 10 of the formula: 

38. An imidazole derivative as claimed in Claim 1 substantially as hereinbefore described with reference to the Examples.

39. A pharmaceutical composition comprising an imidazole derivative as claimed in any preceding claim and a pharmaceutically acceptable carrier.

40. A pharmaceutical composition for oral administration containing, as active ingredient, an imidazole derivative as claimed in any one of Claims 1 to 28 in an amount in the range of about 1 to about 1,000 mg per day per body.

41. A pharmaceutical composition for parenteral administration containing, as active ingredient, an imidazole derivative as claimed in any one of Claims 1 to 38 in an amount in the range of about 0.1 to about 100 mg per day per body.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.